S162. MULTI-MODAL ANALYSIS OF THE EFFECTS OF URBAN UPBRINGING ON BRAIN STRUCTURE: THE FOR2107 COHORT

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Background: Urbanicity has been identified as a major environmental risk factor for schizophrenia as well as other major mental disorders. While initial structural brain imaging studies have pointed to medial and lateral prefrontal cortices being associated with urbanicity during childhood and adolescence, most of these studies have been limited to smaller samples and single analysis methods. The present study used the large ongoing FOR2107 multi-centre study cohort (Kircher et al., 2018) to analyse associations of urban upbringing.
Methods: We analysed a data set of n=625 healthy subjects without a current or previous psychiatric disorder (ascertained through SCID-I interviews), who underwent 3 Tesla MRI scanning, obtaining a high-resolution T1-weighted MPRAGE and a DTI scan. We subsequently also analysed a pilot samples of 42 patients with DSM-IV schizophrenia. We obtained data on urban upbringing (Lederbogen score; Lederbogen et al., 2014) for the first 15 years of life, as well as number of moves. T1 data were pre-processed using CAT12 software, using surface-based morphometric analysis of cortical thickness (CT) with 15 mm smoothing. DTI data were analysed using the TBSS approach in FSL software. We used general linear models to calculate multiple regression analyses using both linear and quadratic (non-linear) associations with urbanicity scores, followed up by analyses of correlations with number of relocations (as unspecific stress factors). Analyses of CT and DTI were each corrected for multiple comparisons using FWE.
Results: In the healthy subject cohort we identified a significant negative linear correlation (p=0.042 FWE cluster-level; p=0.014 peak-level) between urban upbringing scores and cortical thickness (CT) in a right precuneus / posterior cingulate cluster (x/y/z=35;-88;-15), while non-linear analysis identified an additional trend in the left occipital cortex (p=0.073 FWE cluster-level; -17;-100;15). We did not find significant effects for number of relocations/moves. DTI analysis of fractional anisotropy (FA) showed a significant association (all p<0.05 FWE-corrected) for the uncinate fasciculus and inferior fronto-occipital fasciculus. CT analysis in the schizophrenia pilot cohort showed similar effects, but in a more dorsal precuneus cluster (6;-56;45) only at uncorrected levels.
Discussion: Our study identified structural variation in cortical thickness in the precuneus / posterior cingulate cortex of healthy subjects, regions linked to abnormal DMN activity and stress. While the trend-level finding in schizophrenia patients was located in an adjacent cluster, our findings can be interpreted as these medial parietal lobe structure mediating this particular risk factor. Our findings argue against a more wide-spread non-specific effect, as seen in some earlier smaller studies, but points to distinct neuronal network as mediators of this particular risk. The identified brain regions are linked to stress. Unlike previous prefrontal findings, they suggest a new link to the precuneus, a central hub of the default mode network. Given that these effects were observed in clinically healthy subjects, our findings also carry implications for a better understanding of the macro-environment in adolescence.

S163. GLUTAMATERGIC METABOLITES IN THE PSYCHOSIS SPECTRUM: FROM HIGH RISK SAMPLES TO FIRST EPISODE PSYCHOSIS

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Background: The N-methyl-D-aspartate receptor hypofunction model of schizophrenia suggests that dysfunction of these receptors leads to an excess release of glutamate and could explain the brain structural abnormalities characterizing these patients. However, glutamatergic pathways underlying transition to psychosis are yet unclear.
Methods: Youth with recent onset psychosis (FEP), within the first 5 years of disease, individuals with high risk for psychosis (HR) –including participants with psychosis risk syndrome meeting SIPS/SOPS criteria and offspring of parents with bipolar disorder or schizophrenia –, and healthy volunteers, were recruited and scanned with a 3T Siemens scanner. Magnetic resonance spectroscopy was performed using a 2x2x2 cm3 voxel (VOI) placed in the middle frontal region. Ratios of glutamate (Glu), and glutamate + glutamine (Glx) were quantified using LCModel.
Results: 18 adolescents with FEP, 33 HR and 32 healthy controls (HC) were included in the analysis. There were no significant differences between groups in mean age (16.4±2.1 vs 15.7±2.7 vs 16.8±1.9; F=2.0, p=.139), but there were trend-level differences in gender (%females: 33.3% vs 57.6% vs 68.8%; X2=5.9, p=.052). Multivariate models controlling for gender showed a trend-level effect of group in Glu (F=2.9, p=.062), but not in Glx. Post-hoc pairwise contrasts for Glu revealed significantly higher Glu levels in HR individuals (1.38±0.16) compared to FEP (1.27±0.20) and HC (1.31±0.15).
Discussion: Our findings support that increased Glu in the prefrontal cortex may index risk of psychosis from the early stages of the disease, during adolescence. Our observations suggest a possible hyperglutamatergia in premorbid stages that may normalize –or even decrease – after illness onset, possibly related to treatment or compensatory mechanisms. While requiring replication in a larger sample and including follow-up through transition in HR individuals, our findings raise the possibility that abnormal glutamatergic metabolism in the prefrontal cortex could be used as a potential biomarker of illness and putative treatment target.

S164. HIPPOCAMPAL CONNECTIVITY IN YOUTH WITH SCHIZOPHRENIA: COMPARISON WITH PATIENTS WITH NMDA RECEPTOR ENCEPHALITIS AND HEALTHY VOLUNTEERS

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Background: The N-methyl-D-aspartate receptor (NMDAR) hypofunction model of schizophrenia suggests that dysfunction of these receptors could underlie the brain functional abnormalities characterising these patients. In NMDAR encephalitis (NMDARE), which holds clinical similarities with schizophrenia, autoantibodies target NMDARs, predominantly located in the hippocampal region, leading to disrupted glutamatergic transmission. One study so far has described abnormal connectivity between the medial temporal lobe and posterior default mode network regions in patients with NMDARE (Peer et al., 2017), however no study so far has examined brain functional correlates of schizophrenia and NMDARE comparatively.
Methods: Patients with schizophrenia (N=16) and with NMDARE shortly after clinical stabilisation (N=15) were recruited within a tertiary setting, and compared with age and sex-matched healthy volunteers (N=20). All individuals were scanned with a 3T Siemens scanner including a functional resting state sequence, during which individuals were instructed to view a fixation cross. A seed-based analysis was performed using a spherical seed of 4mm located in the left hippocampus (MNI coordinates x =-32, y=-24, x=-14). Only grey matter voxels were considered to obtain the seed average signal. BOLD signal was preprocessed including slice timing, motion correction, spatial smoothing, and frequency filtering, and regressed taken into account movement parameters (rigid transformation, frame displacement, and DVARS). Statistics was performed between the correlation maps including age and sex as covariates. Family-wise error (FWE) was used to correct for multiple comparisons.
Results: Seed to voxel analyses revealed connectivity between the seed and the bilateral thalamus, parahippocampus, precuneus, posterior cingulate, right hippocampus and lateral temporal regions (threshold Fisher's z > 0.28). We first examined differences in connectivity between both patient groups combined and healthy volunteers, which revealed greater connectivity in patients than in controls between the left hippocampus and the left inferior parietal, postcentral and posterior cingulate gyri (pFWE< 0.05). When examining patient groups individually, patients with schizophrenia continued to exhibit significantly greater connectivity between the left hippocampus and left inferior parietal and postcentral region (pFWE< 0.05) and at near trend level in the posterior cingulate (pFWE= 0.15). NMDARE patients also presented near trend level increased connectivity in the posterior cingulate and postcentral gyri (pFWE= 0.10). There were no differences in functional connectivity of the left hippocampus between patients with schizophrenia and with NMDARE.
Discussion: To our knowledge, this is the first study to compare patients with schizophrenia with patients with NMDARE using measures of brain function. We found that, for both conditions, the left hippocampus showed greater connectivity with areas belonging to the posterior default mode network. Connectivity between these regions has been associated with psychotic symptoms in schizophrenia (Lefebvre et al., 2016). Our findings suggest that this alteration could also underlie neuropsychiatric symptoms in NMDARE, and provides further evidence that NMDAR dysfunction may underpin the pathophysiology of schizophrenia.

S165. GLUTAMATERGIC ABNORMALITIES IN EARLY SCHIZOPHRENIA AND BIPOLAR DISORDER MEASURED USING WHOLE-BRAIN SPECTROSCOPY

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Background: Glutamatergic abnormalities in schizophrenia and bipolar disorder gave been identified using proton magnetic resonance spectroscopy (1H-MRS). Although schizophrenia and bipolar disorder are both known to involve extensive brain networks, most MRS studies have been done using single-voxel techniques. In this study we used whole brain 1H-MRS to examine glutamine-plus-glutamate (Glx) in early schizophrenia and bipolar disorder to examine metabolic abnormalities associated with affective and non-affective psychosis and with exposure to antipsychotic medication.
Methods: Three dimensional 1H-MRS was acquired in young schizophrenia (SCZ, N=36, 24 M, 22.8±3.9 years, 19 antipsychotic-naïve and 17 antipsychotic-treated), bipolar (N=13, 5 antipsychotic-naïve and 8 antipsychotic-treated), schizoaffective-bipolar type (N= 3, 2 antipsychotic-naïve and 1 antipsychotic-treated) subjects, and healthy controls (HC, N=29, 17M, 23±4.4yrs). Glx, N-acetylaspartate, choline, myo-inositol and creatine group contrasts from all individual voxels that met spectral quality were analyzed in common brain space (voxel-wise p-threshold=0.001), followed by cluster-corrected alpha value (p<0.05). Bipolar subjects (N=13) and schizoaffective-bipolar type (N=3) were combined (SBP) (N=16, 11M, 21.9±2.9yrs, 7 antipsychotic naïve and 9 antipsychotic-treated).
Results: SCZ subjects compared to HC had lower Glx in the left superior (STG) and middle temporal gyri (16 voxels, p=0.04) and increased creatine in two clusters involving left temporal, parietal and occipital regions (32, and 18 voxels, p=0.02 and 0.04, respectively). Antipsychotic-treated and naïve SCZ had similar Glx reductions (8/16 vs 10/16 voxels respectively, but p's>0.05). However, creatine was higher in antipsychotic-treated vs HC's in a larger left hemisphere cluster (100 voxels, p=0.01). Also in treated SCZ, choline was increased in left middle frontal gyrus (18 voxels, p=0.04). Finally, in antipsychotic-naive SCZ, NAA was reduced in right frontal gyri (19 voxels, p=0.05) and myo-inositol was reduced in the left cerebellum (34 voxels, p=0.02). SBP subjects had no significant differences from HC in any area of the brain for any of the metabolites at a voxel-wise p-threshold of 0.001. A cluster of reduced Glx was found at in the right cuneus and precuneus (276 voxels, p=0.05) using a less stringent voxel-wise p-threshold of p< 0.05.
Discussion: Data-driven spectroscopic brain examination supports the presence of reductions in Glx in the left STG early in the course of schizophrenia; this was not seen in individuals with bipolar symptoms. A trend toward decreased Glx in the right cuneus and pre-cuneus in bipolar and schizoaffective patients is consistent with previous findings of abnormal function in this area. The left STG may be a critical target for postmortem and neuromodulation studies in schizophrenia studies.

S166. EFFECTIVE CONNECTIVITY OF FRONTOSTRIATAL SYSTEMS IN FIRST-EPISODE PSYCHOSIS

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Background: Neuroimaging studies have found dysconnectivity of frontostriatal circuits across a broad spectrum of psychotic symptoms. However, it is unknown whether dysconnectivity within frontostriatal circuits originates from disrupted bottom-up or top-down control signaling within these systems. Here, we used dynamic causal modelling (DCM) to examine the effective connectivity of frontostriatal systems in first-episode psychosis (FEP).